under 35 U.S.C. §102(a) over Peet *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Inventorship

Petitions to correct inventorship are attached. First, under 37 C.F.R. §1.48(b), applicants respectfully request that Joyce Repa be removed as an inventor of the instant application. Dr. Repa's inventive contribution is to claims that have been canceled in light of the restriction requirement and subsequent election. Second, under 37 C.F.R. §1.48(a), applicants petition for the addition of Daniel J. Peet and Jean-Marc A. Lobaccaro. As outlined in the attached declaration, these individuals made substantial contributions to the conception of the presently prosecuted claims.

III. Rejection Under 35 U.S.C. §112, First Paragraph

A. Enablement

Claims 1-11, 21-29, 44 and 45 are rejected under the first paragraph of §112 on the grounds that the specification fails to provide enablement for the full scope thereof. In particular, the examiner argues that the claims are overly broad in the following aspects: (a) claims should be limited to transgenic mice; (b) claims should be limited to mice having a decrease in LXRα protein; and (c) claims should be limited to mice that cannot respond to dietary cholesterol. Applicants traverse the rejection but, in the interest of advancing the prosecution, the claims have been amended to recite points (a) and (c) above.

With regard to point (b), applicants traverse. It would be a very simple matter to create a non-functional LXRα protein by creating a truncation, an internal deletion, or a missense mutations. Yet these mutations would not, by necessity, decrease the amount of LXRα protein. The discussion provided by the examiner at pages 2-7 in no way indicates that such mutations (a) could not be made or (b) would not provide the stated phenotype. As such, applicants submit that the application is fully enabling for mutations other than those which decrease the amount of LXRα. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. Written Description

Claims 1-14, 21-29, 44 and 45 are rejected as lacking written description under §112, first paragraph. Again, the examiner argues that only claims drawn to transgenic mice having a decrease in LXRα protein that cannot respond to dietary cholesterol are enabled. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended as discussed above. In addition, applicants submit that there is no written description issue for mice that contain mutations where merely, alter, truncate or delete LXRα, but do not decrease its level of expression. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1, 2, 21, 27, 44 and 45 are rejected under the second paragraph of §112. First, it is argued that the claims do not differentiate between a wholly introduced non-functional allele or a disrupted gene. This is true – both embodiments are covered by this claim. Further,

applicants submit that this does not render the claims indefinite – it merely provides sufficient breadth to cover both.

Second, it is argued that non-functional is overly broad since LXRα has several domains and, hence, several functions. Applicants traverse, but in order to advance the prosecution, applicants have provided an amendment to the claim that indicates the LXRα defect results in an inability to respond to dietary cholesterol. Of course, this defect may be the result of a variety of different mutations – those that prevent oligomerization, substrate binding, DNA binding, *etc.*

Claims 6 and 7 are rejected as indefinite in the use of the term "nonsense mutation that truncates the LXRα product." Applicants traverse, but have provided amendments that are believed to clarify the claimed subject matter.

Claims 10 and 11 are said to be vague based on the recitation of "contains an alteration in the regulatory region." Applicants traverse, but have provided amendments that are believed to clarify the claimed subject matter.

V. Rejection Under 35 U.S.C. §102

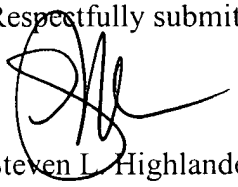
Claims 1-9, 14, 21-29, 44 and 45 stand rejected over Peet *et al.* under §102(a). As discussed above, the inventorship of the instant application has been corrected. In light of these changes, the only difference between the inventorship of the instant application and the authorship of the Peet *et al.* paper is the inclusion of Ma, Janowski and Hammer as coauthors. As explained in the attached declaration of Dr. David Mangelsdorf, these individuals did not

contribute to the conception of subject matter included in the Peet *et al.* paper, and now claimed in the instant application. Therefore, it is believed that Peet *et al.* is not "by another," and as such, does not qualify as prior art under 35 U.S.C. §102(a). Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

VI. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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Date: May 7, 2001

MARKED UP COPY OF CLAIMS

1. (Amended) A [non-human] transgenic [mammal] mouse, the cells of which comprise at least one [non-functional] endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol.

2. (Amended) The [non-human] transgenic [mammal] mouse of claim 1, wherein said cells comprise two [non-functional] endogenous LXRα alleles that lack the capacity to respond to dietary cholesterol.

4. (Amended) The [non-human] transgenic [mammal] mouse of claim 1, wherein said [non-functional] endogenous LXRα allele contains an interruption in the LXRα coding sequence.

5. (Amended) The [non-human] transgenic [mammal] mouse of claim 2, wherein said [non-functional] endogenous LXRα alleles both contain an interruption in the LXRα coding sequences.

6. (Amended) The [non-human] transgenic [mammal] mouse of claim 1, wherein said [non-functional] endogenous LXRα allele contains a nonsense mutation that truncates the corresponding encoded LXRα [product] polypeptide.

7. (Amended) The [non-human] transgenic [mammal] mouse of claim 2, wherein said [non-functional] endogenous LXRα alleles both contain a nonsense mutation that truncates the corresponding encoded LXRα [products] polypeptide.

8. (Amended) The [non-human] transgenic [mammal] mouse of claim 1, wherein said [non-functional] endogenous LXRα allele contains a deletion of LXRα coding sequences.

9. (Amended) The [non-human] transgenic [mammal] mouse of claim 2, wherein said [non-functional] endogenous LXRα alleles both contain a deletion of LXRα coding sequences.

10. (Amended) The [non-human] transgenic [mammal] mouse of claim 1, wherein said [non-functional] endogenous LXRα allele contains [an alteration] a mutation in the 5' regulatory region of the LXRα gene.

11. (Amended) The [non-human] transgenic [mammal] mouse of claim 2, wherein said [non-functional] endogenous LXRα alleles both contain [an alteration] a mutation in the 5' regulatory region of the LXRαs.

12. (Amended) The [non-human] transgenic [mammal] mouse of claim 10, wherein said alteration comprises substitution of an inducible/repressable promoter for the endogenous LXRα promoter.

13. (Amended) The [non-human] transgenic [mammal] mouse of claim 11, wherein said alterations comprise substitution of inducible/repressable promoters for both of the endogenous LXRα promoters.

14. (Amended) The [non-human] transgenic [mammal] mouse of claim 1, wherein cells of said mammal further comprise an exogenous selectable marker gene under the control of a promoter active in at least one cell type of said mammal.

21. (Amended) A method for screening a candidate substance for the ability to reduce cholesterol levels in a mammal comprising:

(a) providing a [non-human] transgenic [mammal] mouse, the cells of which comprise at least one [non-functional] endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol;
(b) treating said [mammal] mouse with said candidate substance; and
(c) monitoring a cholesterol-related phenotype in said [mammal] mouse,

wherein a reduction in said cholesterol-related phenotype in [mammals] said mouse treated with said candidate substance, as compared to a similar [mammal] mouse not treated with said candidate substance, indicates that said candidate substance reduces cholesterol levels.

24. (Amended) The method of claim 21, wherein said [mammal] mouse is maintained on a high cholesterol diet.

25. (Amended) The method of claim 21, wherein said [mammal] mouse further is treated with an agent that blocks cholesterol biosynthesis.

26. (Amended) The method of claim 21, wherein said cells comprise two [non-functional] endogenous LXRα alleles that lack the capacity to respond to dietary cholesterol.

27. (Amended) A method for screening a candidate substance for the ability to increase bile acid synthesis in a mammal comprising:

(a) providing a [non-human] transgenic [mammal] mouse, the cells of which comprise at least one [non-functional] endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol;
(b) treating said [mammal] mouse with said candidate substance; and
(c) monitoring a bile acid-related phenotype in said [mammal] mouse,

wherein an increase in said bile acid-related phenotype in [mammals] said mouse treated with said candidate substance, as compared to a similar [mammal] mouse not treated with said candidate substance, indicates that said candidate substance increases bile acid synthesis.

44. (Amended) A transgenic mouse cell which comprises at least one [non-functional] endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol.

45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two [non-functional] endogenous LXRα alleles that lack the capacity to respond to dietary cholesterol.